Summary of Safety and Effectiveness Data

I. General Information

Product Generic Name: Drug-Eluting Coronary Stent System (NIQ)

Product Trade Name: CYPHER™ Sirolimus-eluting Coronary Stent mounted on either RAPTOR™ Over-the-Wire or RAPTORRAIL® Rapid Exchange Delivery Systems

Applicant's Name and Address: Cordis Corporation
7 Powder Horn Drive
Warren, NJ 07059

PMA Number: P020026

Date of Panel Recommendation: October 22, 2002

Date of Notice of Approval to Applicant: April 24, 2003

II. Indications for Use

The CYPHER™ Sirolimus-eluting Coronary Stent is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete *de novo* lesions of length ≤ 30mm in native coronary arteries with reference vessel diameter of ≥ 2.5 mm to ≤ 3.5 mm.

III. Contraindications

Use of the Cypher™ Sirolimus-eluting Coronary Stent System (CYPHER™ Stent) is contraindicated in the following patient types:

- Patients with a hypersensitivity to sirolimus or its derivatives.
- Patients with a known hypersensitivity to polymethacrylates or polyolefin copolymers (see Details in **Section V – Product Description**, below)

Coronary artery stenting is contraindicated for use in:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon.

IV. Warnings and Precautions

The warnings and precautions can be found in the CYPHER™ Stent labeling (www.fda.gov/cdrh/mda/docs/p020026.html).

V. Product Description

The CYPHER™ Sirolimus-eluting Coronary Stent (CYPHER™ Stent) is a combination product comprised of two regulated components: a device (a Bx VELOCITY coronary stent system) and a drug component (a formulation of sirolimus in a polymer coating). The characteristics of the CYPHER™ Stent are described in **Table V-1**.

Table V-1: CYPHER™ Stent System Product Description

	CYPHER™ Stent on Raptor™ Over-the-Wire (OTW) Stent Delivery System	CYPHER™ Stent on RaptorRail® Rapid Exchange (RX) Stent Delivery System
Available Stent Lengths, unexpanded (mm)	8, 13, 18, 23, 28, 33	8, 13, 18, 23, 28, 33
Available Stent Diameters (mm)	2.50, 2.75, 3.00, 3.50	2.50, 2.75, 3.00, 3.50
Stent Material & Geometry	A 316L stainless steel Bx VELOCITY stent; Six circumferential cells (2.50 – 3.00 mm stents) or Seven circumferential cells (3.50 mm stents)	
Drug Component	A coating of non-erodible polymers loaded with sirolimus in a formulation applied to the entire surface (i.e., luminal and abluminal) of the stent with a maximum nominal drug content of 314 µg on the largest stent (3.50 x 33mm)	
Delivery System Usable Length	145 cm	137 cm
Delivery System Y-Adapter Ports	Y-Connector [Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen – designed for guidewire ≤ 0.014" (0.36 mm).]	Single access port to the inflation lumen. A guidewire exit port is located at 28 cm from the tip. Designed for guidewire ≤ 0.014" (0.36 mm).
Stent Delivery Balloon	Single-layer nylon, nominally 2 mm longer than the stent, with two platinum-iridium radiopaque marker bands.	
Balloon Inflation Pressure	Nominal Inflation Pressure: 11 atm (1115 kPa); Rated Burst Pressure: 16 atm (1621 kPa)	
Guiding Catheter Inner Diameter	≥ 0.067" (1.7 mm)	≥ 0.056" (1.4 mm) for 2.50 – 3.00 mm ≥ 0.067" (1.7 mm) for 3.50 mm
Catheter Shaft Outer Diameter	3.3F (1.10 mm) proximally 2.7F (0.90 mm) distally	2.3F (0.75 mm) proximally 2.6F (0.85 mm) distally (∅ up to 3.00 mm) 2.9F (0.95 mm) distally (∅ > 3.00 mm)

A. **Device Component Description**

The device component consists of the Bx VELOCITY™ balloon-expandable coronary stent pre-mounted onto a stent delivery system (SDS), either the Raptor™ Over-the Wire (OTW) or the RaptorRail® Rapid Exchange (RX). The Raptor™ OTW delivery system was previously approved for deployment of the uncoated Bx VELOCITY™ stent in P0900043/S20 (approved May 11, 2000) and P900043/S25 (approved February 1, 2001). The RaptorRail® RX delivery system was previously approved for deployment of the uncoated Bx VELOCITY™ stent in P0900043/S26 (approved April 6, 2001) and P900043/S27 (approved September 7, 2001).

The range of stent diameters is made possible by varying the number of circumferential "cells" on the stent. The 2.5 and 3.0mm diameter 316L stainless steel stents have six circumferential cells, whereas the 3.5 mm diameter 316L stainless steel stents have seven circumferential cells. The stent is crimped on various size delivery catheter balloons, which are sized from 2.5 to 3.5 mm.

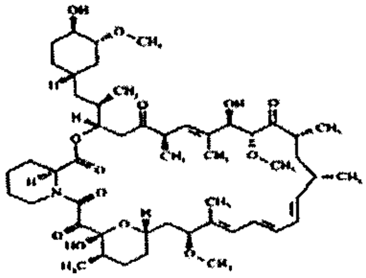
B. **Drug Component Description**

The drug component of the CYPHER™ Stent consists of sirolimus (the active ingredient) and non-erodible polymer carriers (inactive ingredients).

B.1 Sirolimus

The active pharmaceutical ingredient in the CYPHER™ Stent is sirolimus (also known as rapamycin). Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of sirolimus is (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4*H*,6*H*,31*H*)-pentone. Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.2.

The chemical structure of sirolimus is shown below:

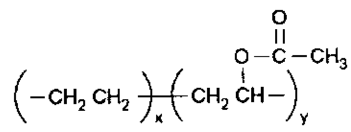


Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile. Refer to **Table V-2** for the nominal dosages of sirolimus on the CYPHER™ Stents.

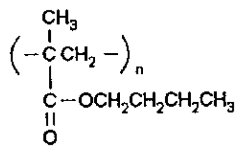
B.2 Inactive Ingredients

The inactive ingredients in the CYPHER™ Stent contain parylene C and the following two non-erodible polymers: polyethylene-co-vinyl acetate (PEVA) and poly n-butyl methacrylate (PBMA). A combination of the two polymers mixed with sirolimus (67%/33%) makes up the basecoat formulation which is applied to a parylene C treated stent. A drug-free topcoat of PBMA polymer is applied to the stent surface to control the release kinetics of sirolimus. The drug/polymer coating is adhered to the entire surface (i.e., luminal and abluminal) of the stent. The structural formulae of the polymer subunits are shown below:

PEVA



PBMA



Parylene C

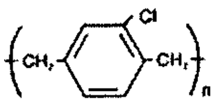


Table V-2: CYPHER™ Stent System Product Matrix & Sirolimus Content

Product Code		Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Sirolimus Content (µg)	Product Code		Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Sirolimus Content (µg)
OTW	RX				OTW	RX			
CWS08250	CXS08250	2.50	8	71	CWS23250	CXS23250	2.50	23	190
CWS08275	CXS08275	2.75	8	71	CWS23275	CXS23275	2.75	23	190
CWS08300	CXS08300	3.00	8	71	CWS23300	CXS23300	3.00	23	190
CWS08350	CXS08350	3.50	8	83	CWS23350	CXS23350	3.50	23	221
CWS13250	CXS13250	2.50	13	111	CWS28250	CXS28250	2.50	28	229
CWS13275	CXS13275	2.75	13	111	CWS28275	CXS28275	2.75	28	229
CWS13300	CXS13300	3.00	13	111	CWS28300	CXS28300	3.00	28	229
CWS13350	CXS13350	3.50	13	129	CWS28350	CXS28350	3.50	28	268
CWS18250	CXS18250	2.50	18	150	CWS33250	CXS33250	2.50	33	268
CWS18275	CXS18275	2.75	18	150	CWS33275	CXS33275	2.75	33	268
CWS18300	CXS18300	3.00	18	150	CWS33300	CXS33300	3.00	33	268
CWS18350	CXS18350	3.50	18	175	CWS33350	CXS33350	3.50	33	314

C. Mechanism of Action

The mechanism (or mechanisms) by which a CYPHER™ Stent affects neointima production as seen in clinical studies has not been established. Sirolimus inhibits T-lymphocyte activation and smooth muscle and endothelial cell proliferation in response to cytokine and growth factor stimulation. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12). The sirolimus-FKBP-12 complex binds to and inhibits the activation of the mammalian Target of Rapamycin (mTOR), leading to inhibition of cell cycle progression from the G1 to the S phase.

VI. Alternative Practices and Procedures

Treatment of patients with coronary artery disease may include exercise, diet, drug therapy, percutaneous coronary interventions (i.e., balloon angioplasty, atherectomy, stenting with other commercially available stents) and coronary artery bypass graft surgery (CABG).

VII. Marketing History

The CYPHER™ Sirolimus-eluting Coronary Stent is commercially available in the following countries:

- Argentina
- Australia
- Brazil
- Canada
- Chile
- China
- Columbia
- Costa Rica
- Czech Republic
- Dominican Rep.
- Ecuador
- Egypt
- El Salvador
- European Community
- Guatemala
- Honduras
- Hong Kong
- Hungary
- India
- Indonesia
- Iran
- Israel
- Korea
- Lebanon
- Malaysia
- Mexico
- New Zealand
- Nicaragua
- Pakistan
- Panama
- Paraguay
- Peru
- Philippines
- Poland
- Russia
- Singapore
- Slovak Republic
- Slovenia
- South Africa
- Sri Lanka
- Thailand
- Turkey
- United Arab Emirates
- Uruguay
- Venezuela
- Vietnam

As of March 31, 2003, approximately 90,000 CYPHER™ Stents have been distributed outside the United States.

The CYPHER™ Stent has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the product.

VIII. Summary of Nonclinical Studies

A series of nonclinical laboratory studies were performed – those related to the stent and stent delivery system (i.e., stent mounted on either the Raptor™ OTW stent delivery system or the RaptorRail® RX stent delivery system), the polymer substances (i.e., the PEVA/PBMA/parylene C coating), the drug substance (i.e., sirolimus) and the finished combination product (i.e., CYPHER™ sirolimus-eluting coronary stent).

A. Biocompatibility Studies

A series of GLP and non-GLP biocompatibility tests and USP Enhanced Physiochemical Testing were conducted to demonstrate that the components of the CYPHER™ Stent System are non-toxic. Tests were conducted on ethylene oxide-sterilized bare metal stents, stent delivery systems, polymer-only coated stents or stainless steel (SS) coupons. These test articles were processed in the same manner as the finished CYPHER™ product, except that where polymers were present, the drug substance, sirolimus, may not have been included in the polymer coating. With the exception of the inclusion of the drug substance, the surface treatment, coating processing, amount of coating per unit area, and sterilization processes were equivalent for both the stents and coupons utilized during this testing. An additional series of biocompatibility tests were conducted where the amount of polymer coating was tripled. In all of these test systems, the materials were non-reactive and produced no greater response than the negative control employed in each test system.

All biocompatibility testing was conducted in accordance with:

- Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices; published by the Interventional Cardiology Devices Branch, Division of Cardiovascular, Respiratory and Neurology Devices, Office of Device Evaluation in May 1995.
- ISO 10993 – 1, Biological Evaluation of Medical Devices: Evaluation and Testing.

The GLP and non-GLP biocompatibility studies are summarized in **Table VIII-1**.

Table VIII-1: Biocompatibility Test Summary

Test Name	Description of Test	Test Article & Results
Cytotoxicity	ISO L929 MEM elution method	▪ Stent & delivery systems: Pass; Non-cytotoxic ▪ Polymer-only coated 316L SS coupon: Pass; non-cytotoxic ▪ 3X polymer-only coated coupon: Pass; non-cytotoxic
	ISO L929 Agarose Overlay (non-GLP)	▪ 3X polymer-only coated stent: Pass; non-cytotoxic
Sensitization	ISO Guinea pig maximation method	▪ Stent & delivery systems: Pass; Non-sensitizing ▪ Polymer-only coated 316L SS coupon: Pass; non-sensitizing
Intracutaneous Reactivity	ISO Intracutaneous Reactivity (rabbit)	▪ Stent & delivery systems: Pass; Non- irritating ▪ Polymer-only coated 316L SS coupon: Pass; Non-irritating
Systemic Toxicity	USP Acute Systemic Injection (mouse)	▪ Stent & delivery systems: Pass; No evidence of systemic toxicity ▪ Polymer-only coated 316L SS coupon: Pass; No evidence of systemic toxicity
Pyrogenicity	ISO Materials-Mediated Pyrogenicity (rabbit)	▪ Stent & delivery systems: Pass; Non- pyrogenic ▪ Polymer-only coated 316L SS coupon: Pass; Non-pyrogenic
Hemocompatibility /Hemolysis	*In Vitro* Platelet/Leucocyte Count	▪ SS coupon: Pass ▪ Polymer-only coated 316L SS coupons: Pass
	Partial Thromboplastin Time	▪ SS coupon: Pass ▪ Polymer-only coated 316L SS coupon: Pass
	In Vitro Thrombogenicity	▪ Stent: Pass ▪ Cypher™ stent: Pass; Less thrombogenic than bare stent
	In Vitro C3a & Sc5b-9 Complement Activation Immunoassay	▪ 3X polymer-only coated stent: Pass; Non-activating
	NIH extract method	▪ Stent & delivery systems: Pass; Non-hemolytic ▪ Polymer-only coated 316L SS coupon: Pass; non-hemolytic
	NIH Direct Contact Method (non-GLP)	▪ 3X polymer-only coated coupon: Pass; non-hemolytic
Implantation	ISO 7-day Intramuscular Implant (rabbit) (non-GLP)	▪ 3X Polymer-only coated stent: Pass
	ISO 14-day Intramuscular Implant (rabbit) (non-GLP)	▪ Polymer-only coated stent: Pass
	3 & 30-day Muscle Flap Implant (rat) (non-GLP)	▪ 3X Polymer-only coated stent: Pass

Test Name	Description of Test	Test Article & Results
Genotoxicity	Bacterial Reverse Mutagenicity Assessment (Ames Assay)	▪ Stent: Pass; Non-mutagenic ▪ Polymer-only coated 316L SS coupon: Pass; Non-mutagenic
	In Vitro Chromosomal Abberation Assay (Hamster Ovary)	▪ Stent: Pass; Non-clastogenic ▪ Polymer-only coated 316L SS coupon: Pass; Non-clastogenic
	Mouse Lymphoma Mutagenesis Assay	▪ Stent: Pass; Non-mutagenic ▪ Polymer-only coated 316L SS coupon: Pass; Non-mutagenic
Leukocyte Activation	*In Vitro* Microchemotaxis Assay (non-GLP)	▪ 3X Polymer-only coated stent: Pass; Not chemotaxic
Volatile Metal Extracts	USP Enhanced Aqueous Extract Analysis	▪ 3X Polymer-only coated coupon: Pass

Since the sponsor did not conduct the traditional battery of ISO-10993 testing on the finished CYPHER™ Stent (i.e., containing the drug substance), sub-chronic toxicity, thrombogenicity, and implantation of the final CYPHER™ product, containing all components and processing, were evaluated in porcine, rabbit and canine models of stent-mediated vascular injury. The significant animal studies are summarized separately in **Section VIII-F – Animal Studies.**

The genotoxicity, carcinogenicity, and reproductive toxicity of CYPHER™ Stents have not been evaluated. However, the genotoxicity, carcinogenicity, and reproductive toxicity of sirolimus have been investigated in bacterial and mammalian cells *in vitro* and in laboratory animals *in vivo*. Formal carcinogenicity testing was not required because sirolimus does not remain on the product longer than six months.

The preclinical and clinical toxicology testing of sirolimus has been conducted by Wyeth-Ayerst. *In vivo* animal and *in vitro* pharmacology and toxicology studies as well as *in vivo* and human pharmacokinetic studies of the drug substance were conducted to provide information about systemic, regional and local toxicity, dose-related toxicity, distribution profiles, end-organ disposition, drug metabolism, and potential drug-drug interactions.

A right to reference Wyeth-Ayerst's NDAs (i.e., drug substance information) was provided by Cordis in support of this application. A right to reference SurModics Inc.'s Device Master File (MAF) (i.e., polymer information) was also provided by Cordis is support of this application. Appropriate information from both of these files was taken into consideration to support the initial safety of the product for the initiation of human clinical trials as well as in the review of this submission.

There is no evidence to suggest that any chemical interactions occur, which would form a new intermediate or molecular entity, between sirolimus or the polymeric carriers used in the CYPHER™ Stents.

Long term biocompatibility of the drug/polymer coating on the stent in humans is unknown.

B. *In Vivo* Pharmacokinetics

B.1 CYPHER™ Sirolimus-eluting Coronary Stent

The pharmacokinetics of sirolimus as delivered by the CYPHER™ Stent has been determined in patients with coronary artery disease after implantation of 1 (n=10) or 2 (n=9) CYPHER™ Stents. The parameters determined from patients receiving 1 and 2 CYPHER™ Stents are provided in **Table VIII-2.**

Table VIII-2: Whole Sirolimus Pharmacokinetic Parameters in Patients after Implantation of CYPHER™ Stents

Number of Stents	Statistic	Dose (μg)	t_{max} (h)	C_{max} (ng/ml)	$T_{1/2}$ (h)	AUC (ng•h/ml)	CL (ml/h/kg)
1 (n = 10)	Mean	161	3.90	0.57	206	127	17.7
	SD	15	2.38	0.12	92	51	7.5
	%CV	9.09	61.0	20.5	44.8	40.3	42.2
	Range	149-178	1-6	0.43-0.77	111-354	58-225	6.22-29.2
2 (n = 9)	Mean	315	3.24	1.05	220	227	17.1
	SD	25	3.59	0.39	106	58	5.3
	%CV	7.84	111	37.4	48.3	25.7	31.2
	Range	299-355	1.05-12.2	0.51-1.66	131-486	149-307	9.31-24.5

t_{max} = time peak concentration occurs; C_{max} = peak blood concentration; $t_{1/2}$=terminal-phase half-life; AUC=area under the concentration-time curve; CL=total blood clearance

The results in **Table VIII-2** show that C_{max} and AUC were closely dose-proportional over a 2-fold range in doses. The blood levels after stent implantation were 10 to 20 fold lower than what was observed after oral administration of sirolimus in either healthy volunteers or transplanted patients. The mean ± SD sirolimus terminal half-life ($t_{1/2}$) after stent implantation for the combined groups (n = 19) was 213 ± 97 h. By comparison, the mean ± SD sirolimus $t_{1/2}$ values after single dose administration of sirolimus by oral solution in healthy subjects (n = 305) and renal transplant patients (n = 81) were 72.9 ± 19.3 h and 58.2 ± 19.2 h, respectively. The apparent discrepancy in half-lives after stent implantation and oral administration is due to the fact that the decline in terminal sirolimus concentrations reflects the release of sirolimus from the stent and not elimination of sirolimus from the body.

B.2 Drug Interactions

Drug interaction studies have not been conducted with the CYPHER™ Stent. Sirolimus is extensively metabolized by cytochrome P450 3A4 (CYP3A4) in the gut wall and liver and undergoes efflux from enterocytes of the small intestine by P-glycoprotein (P-gp). Therefore, absorption and the subsequent elimination of systemically absorbed sirolimus may be influenced by drugs that affect these proteins. Inhibitors of CYP3A4 and P-gp may increase sirolimus levels, while inducers of CYP3A4 and P-gp may decrease sirolimus levels. The pharmacokinetic interaction between orally administered sirolimus and concomitantly administered drugs is described in detail in the IFU. Drug interaction studies have not been conducted with drugs other than ketaconazole, rifampin, diltiazem, or cyclosporine as described in the IFU.

C. *In Vitro* Engineering Testing

Relevant *in vitro* engineering testing, in accordance with the FDA "Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: Intravascular Stents", May 1995, was conducted on the uncoated, bare versions of the Bx VELOCITY™ CSS mounted on either the Raptor™ OTW or RaptorRail® RX delivery catheters, which were approved in P900043/S20, S25, S26 and S27.

Supplementary *in vitro* engineering tests were also performed on the CYPHER™ Stent. Some testing was not repeated since there was no change to the stent substrate or catheter delivery systems, and where the effect of the coating was assumed to be negligible when evaluated against measurement and manufacturing tolerances. In tests that were repeated, values for the CYPHER™ Stent System were compared back to the uncoated system. Values reported for the products tested indicated statistical equivalence.

Additional tests were conducted to support the integrity of the coating on the CYPHER™ Stent and are summarized separately in **Section VIII-D – Coating Characterization Testing**.

The in vitro engineering studies conducted are summarized in **Table VIII-3**. "Pass" denotes that the test results met product specifications and/or the recommendations in the above-referenced guidance document.

Table VIII-3: Stent and Delivery Catheter Engineering Testing

Test	Description of Test & Test Articles	Conclusion
Stent Material Specification Conformance Testing		
Bare Stent Material Analysis	Chemical analysis was conducted on the two stainless steel tubing sizes used to fabricate the six-cell and seven-cell stents. Chemical analysis and inclusion content met the specifications for ASTM F-138.	Pass
Surface Contamination	SEM analysis was conducted to detect evidence of surface contaminants or impurities not removed by cleaning processes. Results of SEM evaluation showed no evidence of contamination above the specified limits.	Pass
Mechanical Properties: Tensile Strength & elongation	Testing was performed to determine the yield strength, ultimate tensile strength and percent elongation of the tubing sizes used to fabricate the stents. The tensile strength and elongation met the product specifications.	Pass
Corrosion Resistance	Corrosion testing was performed as part of the fatigue testing on the bare stent and CYPHER stent to analyze the solution for resistance to corrosion. The results indicated that the corrosion resistance met product specifications.	Pass
Stent Integrity Testing		
Stent Free Area	The percent change in free or open area as a function of the nominal stent diameter was determined for the bare stents. The stents met the product specifications.	Pass
Length Changes Upon Expansion: Stent Foreshortening	The percent change in stent length was measured to determine the amount of length reduction the stent may experience after expansion to the nominal inflation pressure. Foreshortening is calculated by subtracting the expanded length from the length while crimped on the catheter. All CYPHER stents tested met product specifications.	Pass

Test	Description of Test & Test Articles	Conclusion
Stent Expansion Uniformity	Testing was conducted to determine the uniformity of stent expansion along the length of the stent. Units were inflated to nominal inflation pressure, balloon deflated, and measurements of the stent diameter taken along the expanded stent length. All tested CYPHER product was within 10% of the labeled diameter at nominal pressure along the stent length.	Pass
Stent Recoil	Testing was conducted to quantify the amount of stent diameter reduction experienced after removal of the inflated balloon to correlate this parameter to the recommended sizing procedures. The system was inflated to the rated burst pressure (RBP) and the balloon removed. Recoil was calculated by subtracting the internal stent diameter after balloon deflation from the internal stent diameter still mounted on the inflated balloon. The results demonstrated with 95% confidence that at least 95% of the CYPHER Stents tested would not exhibit recoil above the acceptance criteria.	Pass
Radial Strength	Testing was conducted to determine the radial resistance of the CYPHER stent to external compression. The results demonstrated with 95% confidence that at least 95% of the product tested exhibited no evidence of stent collapse below the acceptable limit.	Pass
Stent Expansion/ Crack Initiation	Testing was conducted to determine whether the plastic deformation experienced by the stent during expansion gives rise to crack initiation in the coating. This testing was conducted on the CYPHER stent as part of the fatigue testing.	* See note below
Magnetic Resonance Imaging	The interaction between the CYPHER stent and the magnetic resonance imaging field was not evaluated since there was no change to the stent platform from the bare Bx Velocity stent. The following statement has been included within the Instructions for Use: "An MRI scan should not be performed on a patient after stent implantation until there is adequate neointimal investment of the stent because of a potential for stent migration. For a conventional uncoated 316L stainless steel stent this period is usually considered to be eight weeks. Because of the reduced neointimal formation associated with the CYPHER Stent, the period of vulnerability may be longer, but there is currently insufficient information to provide a specific recommendation."	N/A
Finite Element Analysis (FEA)	An analysis of the bare stent, when expanded beyond the nominal maximum diameter, was conducted to ensure that the stent would not fail due to fatigue (as determined by modified Goodman analysis). The FEA evaluated stent designs 'deployed in a straight or bend configuration' when subjected to loading conditions expected in coronary arteries. With the assumptions used, the analysis predicted that fatigue failures should not occur over 400 million cycles of loading.	N/A
Accelerated Fatigue Testing	An accelerated fatigue study (500 million cycles) was conducted on the bare stent, when expanded beyond the nominal maximum diameter, to demonstrate the ability of the stent design to maintain structural integrity. SEM was also used to assess the surfaces of the bare stent for fatigue-induced surface defects. Accelerated *in vitro* testing (up to 400 million cycles) was also conducted on the CYPHER stent, when expanded beyond nominal diameter. Test results indicated that the coating did not impact the structural	* See note below

Test	Description of Test & Test Articles	Conclusion
	integrity of the stent platform. However, stress cracks were observed upon stent expansion pre-fatigue testing which increased upon fatigue testing duration.	
Stent Radiopacity	Testing was conducted on the bare metal stent as the addition of the coating did not add or detract from the radiopacity of the stent in clinical use.	Pass
Stent/Catheter Delivery System Testing		
Dimensional Verification	Testing was conducted on the stent, delivery systems and stent/delivery systems to verify they meet their dimensional specifications. All CYPHER product tested met specifications.	Pass
Maximum Pressure	CYPHER Stent systems, sizes representative of the available product, were tested to determine the burst pressure rating for the delivery systems. The results demonstrated with 95% confidence that at least 99.9% of the balloons will not experience loss of integrity at or below the RBP.	Pass
Stent Diameter vs. Balloon Inflation Pressure (Compliance)	Testing was performed to determine how the diameter of the stent varies when subjected to increasing balloon inflation pressures. The stent sizing results verify that the CYPHER Stent systems are within 10% of the labeled compliance values in the working pressure range for the delivery system.	Pass
Repeat Balloon Inflation	CYPHER Stent systems, across the range of stent/balloon lengths and diameters, were subjected to 20 consecutive inflation cycles to the RPB. The stent/balloon burst results show with 95% confidence, that 90% of the catheters will not experience balloon, shaft, or proximal/distal seal loss of integrity at or below the RBP.	Pass
Balloon Inflation and Deflation Testing	Bx VELOCITY delivery systems across the range of balloon lengths and diameters were tested to verify that the catheter successfully deploys the stent, the balloon deflates within a specified time, and the balloon could be withdrawn from the deployed stent within a specified time. All systems tested met specifications.	Pass
Crossing Profile	CYPHER Stent systems for each diameter balloon were tested to determine the diameter of the crimped stent/balloon profile. All measurements must meet the product specifications with 95% confidence and 95% reliability.	Pass
Stent Retention	Testing was conducted on the CYPHER stent/delivery systems to determine the tensile force required to move a crimped CYPHER stent away from the original crimped position. All tested systems met the stent retention specification. The results demonstrated with 95% confidence that 99% of the CYPHER Stents would not be displaced from the delivery systems below the stent retention specification.	Pass
Bond Strength	The delivery systems were tested to quantify the tensile strength of each catheter joint (balloon distal seal/tip, balloon proximal seal, hub to catheter shaft bond and transition seal) and meets specifications.	Pass
Tip Pulling and Torquing	Testing was conducted on the delivery systems to verify that the force required to break the joints and/or materials in the distal end of the catheter is sufficiently large to assure the integrity of the tip during pulling, pushing or torquing maneuvers.	Pass
Catheter Body Maximum Pressure	Testing was conducted on the bare metal stent/delivery systems to determine the ability of the adhesive bond (hub/shaft), the catheter shaft and the transition seal to withstand the rated burst pressure.	Pass

* Note: Stress cracks were observed in the coatings of all samples both pre- and post-fatigue analysis. Cracks increased in length and width throughout the duration of testing. SEM also showed that changes to the coating surface occur after expansion. The sponsor performed post-fatigue analysis and concluded that the likelihood of particle embolization would be minimal. The phenomenon of delamination of the coating from the stent struts was also noted in several of the animal studies. However, evaluation of the clinical studies provided to support the application did not reveal any negative sequelae that might have arisen from the compromise of coating integrity.

D. Coating Characterization Testing

The following methods were developed to characterize and set initial specifications for the CYPHER™ stent. The coating characterization testing conducted on the CYPHER™ Stent is summarized in **Table VIII-4**.

Table VIII-4: Coating Characterization Testing

Test	Description of Test
Material Analysis – Polymer(s)	Polymer components were tested to ensure conformity to raw material specifications and incoming inspection procedures
Chemical Analysis – Polymer(s)	Assays were conducted to determine Mw, Mn, polydispersity, monomer content, presence/formation of oligomers & free monomers
Chemical Analysis – Drug	Drug substance was tested to ensure conformity to incoming Certificate of Analysis
Drug Content	Assay was conducted to quantitatively determine the total amount of the drug substance, sirolimus, on the CYPHER Stent.
Dose Density	Dose per unit area was calculated.
Drug Content Along Stent Length	Testing was conducted to characterize the distribution of drug content along the length of the CYPHER Stent.
Coating Uniformity / Reproducibility	Testing was conducted to determine the reproducibility of coating distribution from stent to stent and batch to batch.
Coating Thickness	Testing was conducted to describe the coating thickness along the length of the stent.
Impurities / Degradation Products	Assays were conducted to quantitatively determine the type and amount of impurities and degradation products on the CYPHER Stent.
In Vitro Elution	Assay was developed to measure the *in vitro* release kinetics of sirolimus off the CYPHER Stent.
Particulates	Particulate levels, after stent deployment, were determined for the CYPHER Stent to be within the USP <788> specification for small volume injections.

E. Chemistry, Manufacturing & Controls (CMC) Testing

Where applicable, International Conference on Harmonization (ICH) Guidelines were followed for the testing routinely performed on the CYPHER™ Stent as part of CMC. This testing is summarized in **Table VIII-5**. Information to support the stability of the CYPHER™ Stent is summarized separately in **Section VIII-G – Stability/Shelf Life**, below.

Table VIII-5: CMC Release Testing

Test	Description of Test
Material Analysis – Polymer(s)	Polymer components were tested to ensure conformity to specifications. The polymer(s) met specifications prior to utilization in finished goods.
Drug Identity	Assays were conducted to verify the identity of the drug substance, sirolimus, on the CYPHER Stent. The product met specifications established for finished goods release.
Drug Content/Impurities	Assays were conducted to quantitatively verify the amount of drug & type of impurities on the CYPHER Stent. The product met specifications established for finished goods release.
Drug Content Uniformity	Multiple CYPHER Stents were assayed to verify the uniformity of the drug content between individual CYPHER Stents was within specifications established for finished goods release.
Residual Solvents	Assay was conducted on CYPHER Stents to verify that residual levels of solvents used in the manufacturing process were below acceptable limits established for finished goods release.
In Vitro Elution	The *in vitro* release profile of sirolimus was measured for the CYPHER Stent. Specifications were based on the elution characteristics of stents evaluated in the clinical investigation.
Particulates	Particulate levels were monitored to verify that they remain below acceptable levels as established in the product specifications.

F. Animal Studies

Detailed arterial histopathology and histomorphometry are not obtainable through human clinical trials, so a series of *in vitro* and *in vivo* studies were conducted to evaluate safety, efficacy (proof of concept), and overall product performance.

Prior to conducting GLP studies, the sponsor performed a series of non-GLP feasibility studies evaluating a variety of sirolimus-eluting stent formulations (e.g., various drug dosages, drug concentrations, systems without drug-free topcoat, etc.), polymer-coated control stents and/or bare metal control stents. These studies were conducted in coronary arteries of pigs, or iliac arteries of rabbits. These studies served as the basis for the dose selection for the CYPHER™ Stent used in the clinical studies.

The intravascular safety and biocompatibility of sirolimus-eluting stents were evaluated in a series of animal studies in a porcine model of stent-mediated vascular injury. The results of these tests support the safety and biocompatibility of the CYPHER™ Stent. Summaries of the major animal studies performed to support product safety are included in **Table VIII-6**.

Table VIII-6: Summary of Major Supportive Animal Studies

Study #	Stent Design	Type of Animals	Follow-up Duration	Endpoints / Purpose
ETP-2-002233-R	Test Article: CYPHER Stents (3.5 x 18mm) & Control: BMS GLP: Yes	Yucatan miniswine (LAD, LCX, RCA) One stent/vessel	3, 30, 90 & 180 days	Histological & histomorphometric evaluations coupled with angiography – Chronic vascular response & acute delivery
ETP-12-002351-P	Test Article: CYPHER Stents (3.5 x 8mm)	Domestic swine (LAD, LCX, RCA) One stent/vessel	24 hrs, 3, 8, 14 & 29/30 days	Evaluation of drug release rate, arterial drug levels & systemic drug levels over time
ETP-12-002344-R	Test Article: CYPHER Stents (3.5 x 18mm) Controls: BMS & polymer coated	Porcine coronaries (LAD, LCX, RCA) One stent/vessel	3, 14, 30 & 90 days	Evaluation of degree of re-endothelialization by SEM (also included immunohistochemistry & TEM)
913-004	Test Articles: 5 different sirolimus-eluting Bx Velocity Stents (3.5 x 18mm) Controls: BMS & polymer coated	Domestic swine (LAD, LCX, RCA) One stent/vessel	30 day histology Blood levels measured at 1-5 minutes, 30 minutes, 1, 6, 24, 72 hours & 7 days post-implant	Evaluation of the dose-response relationship for various sirolimus-eluting Bx Velocity stents
913-003	Test Article: High dose sirolimus-eluting Bx Velocity stent (3.5 x 18mm)	Domestic swine (LAD, LCX, RCA) One stent/vessel	30 day histology	Evaluation of high dose sirolimus-eluting stent (~7X safety margin)
* 913-023	Test Article: CYPHER Stents & high-dose sirolimus-eluting Bx Velocity Stents (3.5 x 18mm) Controls: BMS & exaggerated polymer coated GLP: Yes	Yucatan miniswine (LAD, LCX, RCA) Two stents/vessel	30, 90 & 180 days	Histological & histomorphometric evaluation of exaggerated dose & overlapping exaggerated dose stents coupled with angiography – Chronic vascular response

BMS = bare metal stent = Bx VELOCITY for these studies
* This study was completed as a condition of PMA approval.

G. Stability/Shelf Life

Site-specific stability studies were conducted to establish a shelf life/expiration date for the CYPHER™ Stent. Testing to establish package integrity and functional testing of the stent system were conducted on aged product. Testing evaluation included drug identity, assay, degradants, *in vitro* elution, particulates, sterility, drug content uniformity, residual solvents and endotoxins. Appropriate engineering tests were also repeated on aged product and compared to baseline to ensure that the CYPHER™ Stent performed acceptably. The data generated support a shelf life of 6 months.

A GLP polymer stability study was conducted to establish the chemical stability of the main inactive ingredients in the CYPHER™ Stents. The stability of PEVA and PBMA were tested in oxidation and hydrolytic environments, following ISO 10993-13 guidelines. A literature review was also conducted to support that it is unlikely that these components will breakdown unless exposed to extremely high temperatures.

H. Sterilization

The CYPHER™ Stent System is sterilized using Ethylene Oxide (EtO) sterilization, and has been validated per AAMI/ISO 11135:1994 "Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization."

Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}.

The amount of bacterial endotoxins was verified to be within the specification limit for CYPHER™ Stents.

IX. Overview of Clinical Studies

The principal safety and efficacy evidence for the CYPHER™ Stent came from three clinical studies: the SIRIUS trial, the RAVEL trial, and the First-In-Man study. All three of these studies evaluated the performance of the CYPHER™ Stent in patients with symptomatic ischemic disease due to *de novo* lesions in native coronary arteries. Major study characteristics are summarized below and in **Table IX-1**.

The SIRIUS and RAVEL trials were multi-center, double-blind, randomized clinical trials that compared the CYPHER™ Stent to a Control consisting of an uncoated 316L stainless steel stent (the Bx VELOCITY™ Stent). Eligibility was based on visual estimates of vessel diameter and lesion length. Following treatment, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 2 or 3 months, depending on the study. The SIRIUS trial was a large study with a primary clinical endpoint of target vessel failure at 9 months. Angiographic follow-up was scheduled for a majority of patients at 8 months. The RAVEL trial was a smaller study with a primary angiographic endpoint of late loss at 6 months. Clinical follow-up through one year is available for both trials, and follow-up through five years is planned.

The First-In-Man study was a small, non-randomized, initial feasibility study that involved angiographic and clinical follow-up. Its primary value is that it provides the longest available follow-up information, through 2 years.

Table IX-1: Clinical Study Comparison

	SIRIUS (Pivotal)	RAVEL (Supportive)	First-In-Man (Feasibility)
Study Type	Multi-center (n=53), prospective, randomized	Multi-center (n=19), prospective, randomized	Multi-center (n=2) Non-randomized
Number of Patients	1058 (533 CYPHER™ Stent, 525 Control)	238 (120 CYPHER™ Stent, 118 Control)	45 (30 CYPHER™ Stent, 15 other)
Lesion Criteria	*De novo* lesion in native coronary artery ≥ 2.5 to ≤ 3.5 mm in diameter, lesion 15 to 30 mm in length and coverable with 2 stents	*De novo* lesion in native coronary artery ≥ 2.5 to ≤ 3.5 mm in diameter, lesion coverable by one 18 mm stent	*De novo* lesion in native coronary artery ≥ 3.0 to ≤ 3.5 mm diameter, lesion coverable by one 18 mm stent
Product Used	CYPHER™ Sirolimus-eluting Coronary Stent on Raptor™ OTW Stent Delivery System	CYPHER™ Sirolimus-eluting Coronary Stent on Raptor® RX Stent Delivery System	CYPHER™ Sirolimus-eluting Coronary Stent on Raptor™ OTW Stent Delivery System
Antiplatelet Therapy	Aspirin indefinitely, and Ticlopidine or Clopidogrel 3 months	Aspirin indefinitely, and Ticlopidine or Clopidogrel 2 months	Aspirin indefinitely, and Ticlopidine or Clopidogrel 2 months
Follow-up	8 months angiographic 9 months clinic 1, 3, 6, 12 months and 2, 3, 4 and 5 years telephone F/U	6 months angiographic 1 and 6 month clinic 12 months and 2, 3, 4, and 5 years telephone F/U	Brazil: 4, 12, 24 months angio & IVUS The Netherlands: 6 & 8 months angio & IVUS and 24 months clinical F/U

X. Potential Adverse Effects of the Product on Health

A. Observed Adverse Events

Observed adverse event experience comes from three clinical studies, SIRIUS, RAVEL, and First-In-Man. See **Section IX – Overview of Clinical Studies** for more complete descriptions of the study designs.

Principal adverse events for these studies are shown in **Table X-1**. Stent apposition was recorded for the SIRIUS and RAVEL studies and is presented in **Table X-2**.

Table X-1: Principal Adverse Events Observed in Clinical Studies In-Hospital and Out-of-Hospital

	SIRIUS Trial To 360 Days		RAVEL Trial to 720 Days		First in Man to 720 Days
	CYPHER™ Stent (N=533)	Control Stent (N=525)	CYPHER™ Stent (N=120)	Control Stent (N=118)	CYPHER™ Stent (N=30)
MACE[1]					
In-Hospital	2.4% (13)	1.5% (8)	2.5% (3)	2.5% (3)	6.7% (2)
Out-of-Hospital	6.0% (32)	21.3% (112)	7.5% (9)	17.8% (21)	3.3% (1)
Death					
In-Hospital	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3.3% (1)
Out-of-Hospital	1.1% (6)	0.8% (4)	5.0% (6)	2.5% (3)	0.0% (0)
Myocardial Infarction					
In-Hospital	2.3% (12)	1.5% (8)	2.5% (3)	2.5% (3)	3.3% (1)
Out-of-Hospital	0.8% (4)	1.9% (10)	1.7% (2)	2.5% (3)	0.0% (0)
Q-wave					
In-Hospital	0.4% (2)	0.0% (0)	1.7% (2)	0.8% (1)	0.0% (0)
Out-of-Hospital	0.4% (2)	0.4% (2)	0.0% (0)	0.0% (0)	0.0% (0)
Non Q-wave					
In-Hospital	1.9% (10)	1.5% (8)	0.8% (1)	1.7% (2)	3.3% (1)
Out-of-Hospital	0.4% (2)	1.5% (8)	1.7% (2)	2.5% (3)	0.0% (0)
Emergent CABG					
In-Hospital	0.0% (0)	0.0% (0)	--	--	0.0% (0)
Out-of-Hospital	0.0% (0)	0.0% (0)	--	--	0.0% (0)
Target Lesion Revasc. (TLR)					
In-Hospital	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Out-of-Hospital	4.7% (25)	20.0% (105)	2.5% (3)	13.6% (16)	3.3% (1)
TVR not Target Lesion					
In-Hospital	0.0% (0)	0.0% (0)	0.8% (1)	0.8% (1)	3.3% (1)
Out-of-Hospital	3.6% (19)	6.7% (35)	0.0% (0)	1.7% (2)	3.3% (1)
Target Vessel Failure[2]					
In-Hospital	2.4% (13)	1.5% (8)	2.5% (3)	2.5% (3)	6.7% (2)
Out-of-Hospital to 270 days[3]	6.6% (35)	19.6% (103)	--	--	--
Out-of-Hospital to 360/720 days	7.5% (40)	23.6% (124)	3.3% (4)	19.5% (27)	3.3% (1)
Stent Thrombosis					
In-Hospital	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Out-of-Hospital	0.2% (1)	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Sub-acute Closure					
In-Hospital	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Out-of-Hospital	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Late Thrombosis					
Out-of-Hospital	0.2% (1)	0.6% (3)	0.0% (0)	0.0% (0)	0.0% (0)
CVA					
In-Hospital	0.2% (1)	0.8% (4)	0.0% (0)	0.0% (0)	3.3% (1)
Out-of-Hospital	0.9% (5)	1.3% (7)	0.8% (1)	0.0% (0)	3.3% (1)

[1] MACE is defined as Death, Q wave or non-Q wave MI, Emergency CABG, or Target Lesion Revascularization
[2] Target Vessel Failure is defined as Target Vessel Revascularization, MI or cardiac death that could not be clearly attributed to a vessel other than the target vessel.
[3] TVF at 270 days is the primary endpoint for the SIRIUS study
Tabulated entries are represented as: percentage (number of patients with event)

In the SIRIUS trial, a subset of patients underwent intravenous ultrasound (IVUS) evaluation of the treated lesion immediately after treatment and as part of a scheduled angiographic evaluation at 8 months. In the RAVEL trial, a subset of patients underwent an IVUS study as part of the follow-up angiographic evaluation at 6 months, but there was no baseline IVUS evaluation. In both studies, patients who received the CYPHER™ Stent had a greater frequency of incomplete stent apposition at follow-up than patients who received the control stent (BX VELOCITY™, an uncoated 316L stainless steel stent). From the SIRIUS trial, it appeared that in about half of the cases, the incomplete stent apposition had not been observed immediately after stenting (late incomplete stent apposition). Late incomplete stent apposition was not observed in the control group. There were no clinical adverse events that were related to the occurrence of incomplete stent apposition. Frequencies of incomplete stent apposition are shown in **Table X-2**.

Table X-2: Frequency of Incomplete Stent Apposition

	SIRIUS Trial		RAVEL Trial	
	CYPHER™ Stent	**Control Stent**	**CYPHER™ Stent**	**Control Stent**
Incomplete Stent Apposition Rate at Follow-up	18% (18/101)	9% (7/78)	21% (10/41)	4% (2/27)
Changes from Baseline				
Healed	10% (8/80)	5% (3/61)	--	--
Preserved	8% (6/80)	10% (6/61)	--	--
Late Incomplete Stent Apposition	9% (7/80)	0% (0/61)	--	--

B. Potential Adverse Events

Adverse events (in alphabetical order) that may be associated with the implantation of a coronary stent in native coronary arteries, include but are not limited to:

- Abrupt stent closure
- Acute myocardial infarction
- Allergic reaction
- Aneurysm
- Angina
- Arrhythmias, including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arteriovenous fistula
- Cardiac tamponade
- Coronary Artery Occlusion
- Cardiogenic shock
- Death
- Dissection
- Drug reactions to antiplatelet agents / anticoagulation agents / contrast media
- Emboli, distal (air, tissue or thrombotic emboli)
- Embolization, stent
- Emergent Coronary Artery Bypass Surgery (CABG)
- Failure to deliver the stent to the intended site
- Fever
- Fistulization
- Heart failure
- Hematoma
- Hemorrhage
- Hypotension/Hypertension
- Incomplete Stent Apposition
- Infection, including infection and/or pain at the access site

- Myocardial infarction
- Myocardial ischemia
- Perforation or Rupture
- Pericardial effusion
- Prolonged angina
- Pseudoaneurysm
- Renal failure
- Respiratory Failure
- Restenosis of stented segment
- Rupture of native and bypass graft
- Shock/Pulmonary edema
- Spasm
- Stent compression
- Stent migration
- Stroke/cerebrovascular accident/TIA
- Stent thrombosis (acute, subacute, or late)/occlusion
- Ventricular fibrillation
- Vessel perforation
- Vessel spasm
- Vessel trauma requiring surgical repair or reintervention

Potential adverse events, not captured above, that may be related to sirolimus (following oral administration):

- Abnormal liver function tests
- Anemia
- Arthralgias
- Diarrhea
- Hypercholesterolemia
- Hypersensitivity, including anaphylactic/anaphylactoid type reactions
- Hypertriglyceridemia
- Hypokalemia
- Infections
- Interstitial lung disease
- Leukopenia
- Lymphoma and other malignancies
- Thrombocytopenia

There may be other potential adverse events that are unforeseen at this time.

XI. Summary of Clinical Studies

A. SIRIUS Trial (Pivotal Study)

Purpose: The purpose of the trial was to evaluate the safety and effectiveness of the CYPHER™ Stent in reducing target vessel failure in de novo native coronary artery lesions.

Conclusions: In selected patients, use of the CYPHER™ Stent significantly reduced the rate of target vessel failure (TVF) at 9 months compared to the Control (BX VELOCITY™, an uncoated 316L stainless steel stent). Angiographic lesion characteristics at 8 months were also significantly improved.

Design: This was a multi-center, prospective, randomized, double-blind trial conducted at 53 sites in the U.S. The primary efficacy endpoint was pre-specified to be TVF at 9 months, defined as cardiac death, myocardial infarction, or target vessel revascularization. To be eligible, a patient was required to have a *de novo* ischemic lesion of length 15 mm to 30 mm in a native coronary artery of diameter 2.5 mm to 3.5 mm (using visual estimates). Patients could be treated with up to two overlapping stents to cover the lesion.

Patients were randomized with equal probability to receive either the CYPHER™ stent or the Control. A total of 1101 patients were randomized, and 1058 patients were included in the study results; 533 with CYPHER™ and 525 with Control. A subset of 826 was pre-assigned to have angiographic follow-up at 8 months. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 3 months.

Clinical follow-up through the 12-month (± 2 weeks) endpoint was available on 1027 patients. Angiographic follow-up was obtained on 703 patients. A total of 209 patients had both baseline and follow-up IVUS studies. Clinical follow-up currently is available through one year.

Demography: Baseline characteristics were similar for both treatment arms; factors evaluated included age (mean 62 years), gender (29% female), race (90% Caucasian, 4.3% African American, 3.4% Hispanic, 1.7% Asian, and approximately 0.6% other), diabetes (26%), prior MI (31%), hypertension (68%), hyperlipidemia (74%), ejection fraction (mean 54%), CSS Angina Class (44% III or IV), IIb/IIIa inhibitor use (60%), LAD (44%), LCX (25%), RCA (31%), reference vessel diameter (mean 2.8 mm), minimum lumen diameter (mean 0.97 mm), percent diameter stenosis (mean 65%), and lesion length (mean 14.4 mm). The overall fraction with a smoking history was 23%, but it was slightly lower in the CYPHER™ arm (20%) than in the control arm (26%); smoking history was not found to be a significant predictor of outcome in the trial.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by clinical coordinators at the clinical sites. Angiographic and IVUS outcomes were assessed in a blinded fashion by quantitative analysis at designated central laboratories. An independent Clinical Events Committee adjudicated clinical events, and the trial was monitored by an independent Data and Safety Monitoring Committee.

Results: In selected patients, elective CYPHER™ Stent placement in native coronary *de novo* lesions resulted in a reduction in the incidence of TVF at 9 months compared to Control (8.8% vs. 21.0%, $p < 0.001$). By follow-up angiography at 8 months, there was significantly lower in-stent late loss (0.17 mm vs. 1.00 mm, $p < 0.001$) and mean in-lesion % diameter stenosis was significantly reduced (23.6% vs. 43.2%, $p < 0.001$). There was no evidence of an edge-effect 5 mm proximal or distal to the stent. Examination by IVUS at 8 months showed that neointimal hyperplasia (NIH) volume was significantly reduced in the CYPHER™ arm (4.4 mm^3 vs. 57.6 mm^3, $p < 0.001$), but there was a higher rate of incomplete stent apposition (18% vs. 9%, $p = 0.13$). There were no clinical events related to the occurrence of incomplete stent apposition. Clinical outcomes through 12 months were consistent with the 9 month outcomes. Twenty-eight percent (28%) of the patients in the Cypher arm of the SIRIUS trial received 2 or more (overlapping) stents. The incidence of major adverse cardiac events in these patients was statistically significantly lower than the patients who received an uncoated stent.

Table XI-1 summarizes the principal effectiveness and safety results of the SIRIUS Trial through 360 days. **Figure XI-1** provides the cumulative TVF rates through 360 days.

Table XI-1: SIRIUS: Principal Effectiveness and Safety Results (to 360 Days)

	CYPHER™ Stent (N=533 Patients N=533 Lesions)	Control (N=525 Patients N=531 Lesions)	Difference [95% CI]	P-Value
Effectiveness Measures				
Product Success	**97.9%** (522/533)	**98.7%** (524/531)	-0.7% [-2.3, 0.8]	0.477
Procedure Success*	**97.4%** (519/533)	**98.5%** (517/525)	-1.1% [-2.8%, 0.6%]	0.281
Post-Procedure MLD (mm)				
In-Stent	**2.67±0.40** (528)	**2.68±0.42** (526)	0.00 [-0.05, 0.05]	0.985
In-Lesion	**2.38±0.45** (530)	**2.40±0.46** (526)	-0.01[-0.07, 0.04]	0.643
Post-Procedure %DS				
In-Stent	**5.4%±8.2%** (529)	**6.0%±7.9** (526)	-0.6% [-1.6%, 0.4%]	0.229
In-Lesion	**16.1%±9.7%** (530)	**16.2%±8.5%** (526)	-0.1% [-1.2%, 1.0%]	0.792
Eight-Month Follow-up MLD (mm)				
In-Stent	**2.50±0.58** (349)	**1.69±0.79** (353)	0.82 [0.71, 0.92]	<0.001
In-Lesion	**2.15±0.61** (350)	**1.60±0.72** (353)	0.55 [0.45, 0.65]	<0.001
Eight-Month Follow-up %DS				
In-Stent	**10.4%±16.5%** (349)	**40.1%±25.3%** (353)	-29.7% [-32.9%, -26.5%]	<0.001
In-Lesion	**23.6%±16.4%** (350)	**43.2%±22.4%** (353)	-19.7% [-22.6%, -16.8%]	<0.001
Eight-Month Late Loss (mm)				
In-Stent	**0.17±0.44** (347)	**1.00±0.70** (350)	-0.83 [-0.92, -0.74]	<0.001
In-Lesion	**0.24±0.47** (348)	**0.81±0.67** (350)	-0.57 [-0.66, -0.49]	<0.001
Eight-Month Binary Restenosis				
In-Stent	**3.2%** (11/349)	**35.4%** (125/353)	-32.3% [-37.6%, -26.9%]	<0.001
In-Lesion	**8.9%** (31/350)	**36.3%** (128/353)	-27.4% [-33.2%, -21.6%]	<0.001
Eight-Month Minimum Lumen Area (mm^3)	**5.4±2.1** (101)	**3.9±1.9** (75)	1.5 [0.9, 2.1]	<0.001
Eight-Month NIH Volume (mm^3)	**4.4±6.5** (51)	**57.6±32.7** (45)	-53.2 [-62.5, -43.9]	<0.001
TVF to 9 Months (Primary Endpoint)*	**8.8%** (47/533)	**21.0%** (110/525)	-12.1% [-16.4%, -7.9%]	<0.001
Clinical Endpoints to 270 Days				
TLR-Free †	95.8%	83.2%	12.6% [8.5%, 16.7%]	<0.001
TVR-Free †	93.5%	81.1%	12.4% [8.0%, 16.8%]	<0.001
TVF-Free †	91.1%	78.9%	12.2% [7.5%, 16.8%]	<0.001
MACE-Free †	92.8%	81.0%	11.8% [7.4%, 16.3%]	<0.001
Clinical Endpoints to 360 Days				
TLR-Free †	95.0%	79.5%	15.5% [11.4%, 19.7%]	<0.001
TVR-Free †	92.7%	76.9%	15.8% [11.4%, 20.1%]	<0.001
TVF-Free †	90.1%	74.9%	15.2% [10.6%, 19.9%]	<0.001
MACE-Free †	91.7%	77.4%	14.2% [9.8%, 18.7%]	<0.001
Safety Measures				
In-Hospital MACE*	**2.4%** (13/533)	**1.5%** (8/525)	0.9% [-0.8%, 2.6%]	0.379
Out-of-Hospital MACE to 270 days*	**4.9%** (26/533)	**17.7%** (93/525)	-12.8% [-16.6%, -9.1%]	<0.001
Out-of-Hospital MACE to 360 days*	**6.0%** (32/533)	**21.3%** (112/525)	-15.3% [-19.4%, -11.3%]	<0.001
MACE to 270 days*	**7.1%** (38/533)	**18.9%** (99/525)	-11.7% [-15.7%, -7.7%]	<0.001
MACE to 365 days*	**8.3%** (44/533)	**22.3%** (117/525)	-14.0% [-18.3%, -9.8%]	<0.001
TVF to 270 days (Primary endpoint)*	**8.8%** (47/533)	**21.0%** (110/525)	-12.2% [-16.4%, -7.9%]	<0.001
TVF to 360 days*	**9.8%** (52/533)	**24.8%** (130/525)	-15.0% [-19.5%, -10.5%]	<0.001
Stent Thrombosis to 30 days	**0.2%** (1/533)	**0.2%** (1/525)	0.0% [-0.5%, 0.5%]	1.000
Late Thrombosis to 360 days	**0.2%** (1/533)	**0.6%** (3/525)	-0.4% [-1.1%, 0.4%]	0.371
Subacute Closure	**0.2%** (1/533)	**0.0%** (0/525)	-0.2% [-0.2%, 0.6%]	1.000
Cerebrovascular Accident (CVA) to 360 days	**1.1%** (6/533)	**2.1%** (11/525)	-1.0% [-2.5%, 0.5%]	0.231
Major Bleeding Complications	**3.6%** (19/533)	**3.4%** (18/525)	0.1% [-2.1%, 2.3%]	1.000
Major (Hemorrhagic) Vascular Complications	**1.5%** (8/533)	**2.3%** (12/525)	-0.8% [-2.4%, 0.9%]	0.376
Hematological Dyscrasia to 360 days	**0.6%** (3/533)	**0.8%** (4/525)	0.2% [-1.2%, 0.8%]	0.724

Numbers are % (counts/sample size) or Mean ± SD.

Relative Risk = Sirolimus/BX VELOCITY Stent

SE = Calculated in SAS software using Mantel-Haenszel Method

CI = Confidence Interval

CI = RR•exp(±1.96•SE)

All event data were adjudicated by the independent Clinical Events Committee (CEC). All QCA data were assessed by the Angiographic Core Laboratory. All IVUS data were assessed by the IVUS Core Laboratory.

Lesion Success (Lesion Based) – The attainment of <50% residual stenosis (by QCA), using any percutaneous method (if QCA was not available, the visual estimate of diameter stenosis was used).

Product Success (Lesion Based) – Achievement of a final residual diameter stenosis of <50% (by QCA) using the assigned product only (if QCA was not available, the visual estimate of diameter stenosis was used).

Procedure Success (Lesion Based) – Achievement of a final diameter stenosis of <50% (by QCA) using any percutaneous method, without the occurrence of death, Q-wave or WHO-defined non Q-wave MI, or repeat revascularization of the target lesion during the hospital stay (if QCA was not available, the visual estimate of diameter stenosis was used).

In-Lesion (Within Segment) – In-lesion measurement was defined as the measurements either within the stented segment or within 5 mm proximal or distal to the stent edges.

In-Stent (Within Stent) – In-stent measurement was defined as the measurement within the stented segment.

NIH = Neointimal Hyperplasia

* Events rates in this table included the WHO definition of non-Q wave MI.

WHO-defined non Q-wave MI – Elevation of post-procedure CK levels to >2 times normal with elevated CKMB in the absence of new pathological Q-waves.

† The following survival estimates are by Kaplan-Meier Methods with standard error estimates by Peto formula:

TLR-Free – No target lesion revascularization.

TVR-Free – No target vessel revascularization.

TVF-Free – No cardiac death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization.

MACE-Free – No death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization.

Major Adverse Cardiac Events (MACE) – A composite endpoint comprised of death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization.

Target Vessel Failure (TVF) – A composite endpoint comprised of cardiac death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization

Stent Thrombosis – A 30-day endpoint including subacute closure or unexplained death or Q-wave MI.

Late Thrombosis – Myocardial infarction occurring >30 days after the index procedure and attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and freedom from an interim revascularization of the target vessel.

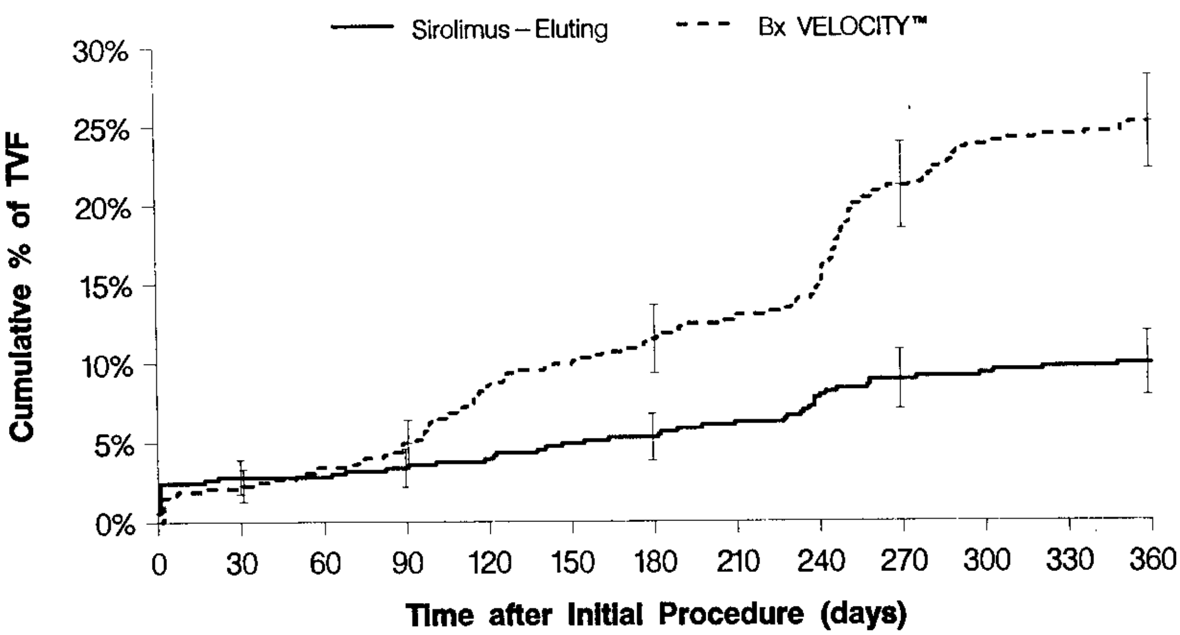
Subacute (Subabrupt) Closure – Abrupt closure that occurred after the index procedure was completed (and the patient left the catheterization laboratory) and before the 30-day follow-up endpoint.

Cerebrovascular Accident (CVA) – Sudden onset of vertigo, numbness, aphasia, or dysarthria due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persisted >24 hours.

Major Bleeding Complications – Bleeding requiring transfusions or associated with hemoglobin drop >5g.

Major (hemorrhagic) Vascular Complication – Hematoma at access site >5 cm; false aneurysm; AV fistula; retroperitoneal bleed; peripheral ischemia/nerve injury; any transfusion required was reported as a vascular complication unless clinical indication clearly other than catheterization complication; and vascular surgical repair.

Figure XI-1: Kaplan-Meier Graph and Life Table to 360 Days – **SIRIUS Cumulative Percentage of Target Vessel Failure**



Error Bars indicate 1.5 Standard Error

	Time after initial procedure (days)												
	0	7	14	30	60	90	120	150	180	210	240	270	360
Sirolimus-Eluting Bx VELOCITY™													
# Entered	533	530	519	519	517	514	509	505	499	496	490	481	474
# Censored	0	1	0	0	3	2	1	1	1	1	1	1	20
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# at risk	533.0	529.5	519.0	519.0	515.5	513.0	508.5	504.5	498.5	495.5	489.5	480.5	464.0
# Events	3	10	0	2	0	3	3	5	2	5	8	6	5
# Events/Month		42.9	0.0	3.8	0.0	3.0	3.0	5.0	2.0	5.0	8.0	6.0	1.7
% with Events	0.6%	2.4%	2.4%	2.8%	2.8%	3.4%	4.0%	4.9%	5.3%	6.2%	7.8%	8.9%	9.9%
SE	0.3%	0.7%	0.7%	0.7%	0.7%	0.8%	0.9%	0.9%	1.0%	1.1%	1.2%	1.2%	1.3%
Bx VELOCITY™													
# Entered	525	525	515	515	513	507	499	475	468	460	450	439	406
# Censored	0	0	0	0	0	0	4	0	1	2	0	2	19
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# at risk	525.0	525.0	515.0	515.0	513.0	507.0	497.0	475.0	467.5	459.0	450.0	438.0	396.5
# Events	0	10	0	2	6	8	20	7	7	8	11	31	20
# Events/Month		42.9	0.0	3.8	6.0	8.0	20.0	7.0	7.0	8.0	11.0	31.0	6.7
% with Events	0.0%	1.9%	1.9%	2.3%	3.4%	5.0%	8.8%	10.1%	11.5%	13.0%	15.1%	21.1%	25.1%
SE	0.0%	0.6%	0.6%	0.7%	0.8%	1.0%	1.3%	1.4%	1.4%	1.5%	1.6%	1.8%	2.0%

Tests Between Groups

Test	Chi-Square	Deg Frdm	P-value
Log-Rank	40.01	1	<0.001
Wilcoxon	38.29	1	<0.001

Standard error estimates by Peto formula.

B. RAVEL Trial (Supportive Study)

Purpose: The purpose of the trial was to evaluate the safety and effectiveness of the CYPHER™ Stent for reducing late loss in *de novo* native coronary artery lesions.

Conclusions: In selected patients, use of the CYPHER™ Stent significantly reduced the rate of in-stent late loss at 6 months compared to the Control (BX VELOCITY™, an uncoated 316L stainless steel stent). Clinical outcomes at 24 months were also significantly improved.

Design: This was a multi-center, prospective, randomized, double-blind trial conducted at 19 sites in Europe, Brazil and Mexico. The primary efficacy endpoint was pre-specified to be in-stent late loss at 6 months. To be eligible a patient was required to have a *de novo* ischemic lesion of a length that could be covered by a single 18 mm stent in a native coronary artery of diameter 2.5 mm to 3.5 mm (using visual estimates).

Patients were randomized with equal probability to receive either the CYPHER™ Stent or the Control stent. A total of 238 patients were randomized; 120 to CYPHER™ and 118 to Control. After the procedure patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 2 months.

Angiographic follow-up at 6 months was obtained on 217 patients. IVUS follow-up (but without baseline studies) was obtained on 110 patients. Clinical follow-up is currently available through 2 years (± 1 month) on 90% of patients.

Demography: Baseline characteristics were similar for both treatment arms; factors evaluated included age (mean 61 years), diabetes (18%), prior MI (36%), hypertension (49%), hyperlipidemia (52%), current smoking (30%), CSS Angina Class (12% III or IV), IIb/IIIa inhibitor use (10%), LAD (50%), LCX (23%), RCA (27%), reference vessel diameter (mean 2.6 mm), minimum lumen diameter (mean 0.95 mm), percent diameter stenosis (mean 64%), and lesion length (mean 9.6 mm). Overall 24% were female, but there were more women in the CYPHER™ arm (30%) than in the Control arm (19%); gender was not a significant predictor of outcome in the trial.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by clinical coordinators at the clinical sites. Angiographic and IVUS outcomes were assessed in a blinded fashion by quantitative analysis at designated central laboratories. An independent review committee adjudicated clinical events, and the trial was monitored by an independent Data and Safety Monitoring Committee.

Results: In selected patients, elective CYPHER™ stent placement in native coronary *de novo* lesions resulted in significantly lower in-stent late loss at 6 months compared to control (-0.01 mm vs. 0.80 mm, $p < 0.001$), and the mean in-lesion % diameter stenosis also was significantly reduced (25.3% vs. 38.7%, $p < 0.001$). There was no evidence of an edge-effect 5 mm proximal or distal to the stent. Examination by IVUS at 6 months showed that neointima volume was significantly reduced in the CYPHER™ arm (1.5 mm^3 vs. 34.3 mm^3, $p < 0.001$), but there was a higher rate of incomplete stent apposition (21% vs. 4%, $p = 0.028$). The rate of target vessel failure by 1 year was lower (4% vs. 20%, $p < .001$).

Table XI-2 summarizes the principal effectiveness and safety results of the RAVEL Trial to 720 days. **Figure XI-2** provides the cumulative TVF rates to 720 days.

Table XI-2: RAVEL: Principal Effectiveness and Safety Results (to 720 days)

	CYPHER™ Stent (N=120)	Control (N=118)	Difference [95% CI]	P-value
Effectiveness Measures				
Procedure Success	**96.7%** (116/120)	**93.1%** (108/116)	3.6% [-2.1%, 9.2%]	0.248
Binary Restenosis Rate	**0.0%** (0/109)	**26.6%** (29/109)	-26.6% [-34.9%, -18.3%]	<0.001
Post-procedure				
MLD in-stent (mm)	**2.43** ± 0.41 (N=120)	**2.41** ± 0.40 (N=116)	0.01 [-0.09, 0.12]	0.705
% DS in-stent	**11.9** ± 5.9 (N=120)	**14.0** ± 6.8 (N=116)	-2.1 [-3.7, -0.5]	0.012
6 month f/u				
MLD in-stent (mm)	**2.42** ± 0.49 (N=109)	**1.64** ± 0.59 (N=109)	0.78 [0.64, 0.93]	<0.001
%DS in-stent	**14.7** ± 6.9 (N=109)	**36.7** ± 18.0 (N=109)	-22.0 [-25.6, -18.4]	<0.001
Late loss (mm)	**-0.01** ± 0.33 (N=109)	**0.80** ± 0.53 (N=108)	-0.81 [-0.93, -0.70]	<0.001
Volume obstruction in-stent (mm)	**1.1** ± 2.5 (N=56)	**26.1** ± 20.2 (N=54)	-25.0 [-30.3, -19.7]	<0.001
TLR-free to 720 days*	97.4%	86.2%	11.2% [3.7%, 18.7%]	0.001
TVR-free to 720 days*	96.6%	83.6%	13.0% [4.9%, 21.1%]	<0.001
TVF-free to 720 days*	94.1%	78.7%	15.4% [6.2%, 24.6%]	<0.001
MACE-free to 720 days*	89.9%	80.4%	9.5% [0.0%, 19.2%]	0.022
Safety Measures				
MACE in-hospital	**2.5%** (3/120)	**2.5%** (3/118)	0.0% [-4.0%, 3.9%]	1.000
MACE out-hospital to 720 days	**7.5%** (9/120)	**17.8%** (21/118)	-10.3% [-18.7%, -1.9%]	0.019
MACE to 720 days	**10.0%** (12/120)	**19.5%** (23/118)	-9.5% [-18.4%, -0.6%]	0.045
Sub-acute occlusion	**0.0%** (0/120)	**0.0%** (0/118)	0.0% [--,--]	--
Stent thrombosis	**0.0%** (0/120)	**0.0%** (0/118)	0.0% [--,--]	--
Late thrombosis	**0.0%** (0/120)	**0.0%** (0/118)	0.0% [--,--]	--
CVA to 720 days	**0.8%** (1/120)	**0.0%** (0/118)	0.8% [-0.8%, 2.5%]	1.000
Major Bleeding Complications to 720 days	**0.8%** (1/120)	**3.4%** (4/118)	-2.6% [-6.2%, 1.1%]	0.211

Numbers are % (counts/available field sample size) or mean ± 1 standard deviation.

CI = Confidence Interval CI = Diff ± 1.96 • SE

SD = Standard Deviation SE = sqrt (p1•q1/n1 + p2•q2/n2)

Procedure success – Successful implantation of study product, attainment of < 30% diameter stenosis by angiographic corelab. Quantitative Coronary Angiography (QCA) determination, and freedom from in-hospital MACE.

%DS – Percent diameter stenosis – value calculated as 100•(1-MLD/RVD) using the mean values from two orthogonal views (when possible) by Quantitative Coronary Angiography (QCA). A 100% DS was imputed for total occlusions if no RVD values were available.

Restenosis Rate – Percent lesions with a follow-up percent diameter stenosis is ≥ 50%.

[1] The following survival estimates are by Kaplan-Meier methods. Standard Error estimates from Peto formula.

TLR–free – No target lesion revascularization

TVR-free – No target vessel revascularization

TVF-free – No cardiac death, target vessel related myocardial infarction or target vessel revascularization

MACE-free – No death, myocardial infarction, target lesion CABG or target lesion Re-PTCA

In-hospital MACE – Death, myocardial infarction (Q-wave and non Q-wave), target lesion CABG or target lesion revascularization prior to hospital discharge as determined by the independent Clinical Events Committee.

Out-of-hospital MACE - Death, myocardial infarction (Q-wave and non Q-wave), target lesion CABG or target lesion revascularization after hospital discharge through the 720 days contact as determined by the independent Clinical Events Committee.

Late loss – Difference MLD after product – MLD at follow-up.

MACE – Major Adverse Cardiac Events: death, myocardial infarction (Q-wave and non Q-wave), target lesion CABG or target lesion revascularization.

Major Bleeding Events – Any intracranial bleeding, cardiac tamponade, bleeding events associated with a decrease in hemoglobin > 5.0 g/dL, transfusion or surgical repair.

MI – Myocardial Infarction: Necrosis of the myocardium, as a result of interruption of the blood supply to the area as in coronary thrombosis. For this study, myocardial infarction was categorized in Q-wave and non Q-wave.

Sub-acute occlusion – New reduced (TIMI 0 or 1) flow at the target vessel as a result of mechanical obstruction, such as dissection or luminal thrombus, occurring after completion of the index procedure but within thirty days of stent deployment.

Stent Thrombosis – Complete thirty-day ischemic endpoint including death, Q-wave MI or subabrupt closure requiring revascularization.

Late Thrombosis – Late Thrombosis was myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel.

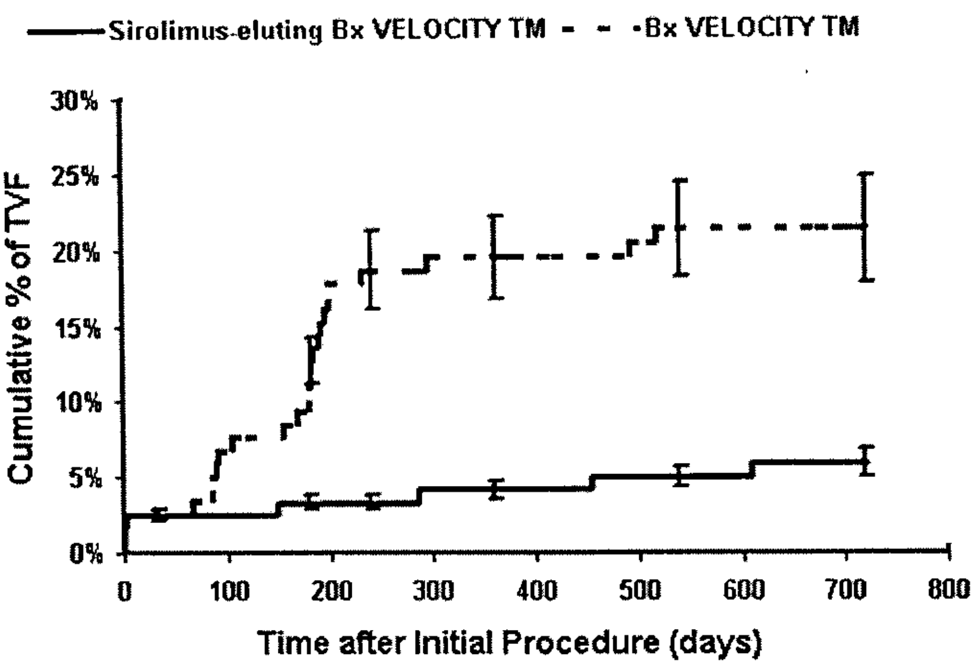
MLD – mean minimal luminal diameter (mm) from two orthogonal views using Quantitative Coronary Angiography (QCA).

RVD – Reference Vessel Diameter: Average of normal segments proximal and distal to the target lesion from two orthogonal views (when available) using QCA

TL = Target Lesion

TV = Target Vessel

Figure XI-2: Kaplan-Meier Graph and Life Table to 720 Days – RAVEL Cumulative Percentage of Target Vessel Failure



Error bars indicate ± 1.5 standard error
Standard Error based on the Peto formula

Target Vessel Failure Life Table Analysis: All Patients Treated (N=238)

Interval ending day	0	2	7	30	60	120	180	240	300	360	420	480	540	600	660	720
Sirolimus-eluting Bx VELOCITY™ (N=120)																
# Entered	120	120	117	117	117	117	117	116	116	115	113	111	110	108	106	101
# Censored	0	0	0	0	0	0	0	0	0	2	2	0	2	2	4	21
# At risk	120	120	117	117	117	117	117	116	116	114	112	111	109	107	104	91
# Events	0	3	0	0	0	0	1	0	1	0	0	1	0	0	1	0
# Events / Month	0	45.0	0.0	0.0	0.0	0.0	0.5	0.0	0.5	0.0	0.0	0.5	0.0	0.0	0.5	0.0
% with Events	0.0	2.5	2.5	2.5	2.5	2.5	3.3	3.3	4.2	4.2	4.2	5.0	5.0	5.0	5.9	5.9
Std. Err. (%)	0.0	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.6
Bx VELOCITY™ (N=118)																
# Entered	118	118	115	115	115	115	109	105	96	93	92	88	88	85	85	85
# Censored	0	0	0	0	0	0	0	0	2	1	4	0	1	0	0	17
# At risk	118	118	115	115	115	115	109	105	95	93	90	88	88	85	85	77
# Events	0	3	0	0	0	6	4	9	1	0	0	0	2	0	0	0
# Events / Month	0	45.0	0.0	0.0	0.0	3.0	2.0	4.5	0.5	0.0	0.0	0.0	1.0	0.0	0.0	0.0
% with Events	0.0	2.5	2.5	2.5	2.5	7.6	11.0	18.6	19.5	19.5	19.5	19.5	21.3	21.3	21.3	21.3
Std. Err. (%)	0.0	0.2	0.2	0.2	0.2	0.7	1.0	1.7	1.8	1.8	1.9	1.9	2.1	2.1	2.1	2.3

Survival Curves Comparison

	Log-Rank P-value	Wilcoxon P-Value
Life-Table Analysis	<0. 001	<0. 001
Kaplan-Meier Analysis	<0. 001	<0. 001

Standard error estimates from Peto formula

C. First-In-Man Study

Purpose: The purpose of this early feasibility study was to evaluate the performance of the CYPHER™ Stent and an alternate formulation sirolimus-eluting stent in *de novo* native coronary artery lesions. This study provides the longest follow-up experience available.

Conclusions: In selected patients, use of the CYPHER™ Stent provided favorable IVUS, angiographic and clinical results through 24 months of follow-up.

Design: This was a non-randomized, open-label study conducted at two sites, one in The Netherlands and one in Brazil. To be eligible, a patient was required to have a *de novo* ischemic lesion of a length that could be covered by a single 18 mm stent in a native coronary artery of diameter 3.0 mm to 3.5 mm (using visual estimates). A total of 45 patients were treated, of which 30 received the CYPHER™ Stent and 15 received an alternative formulation sirolimus-eluting stent. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel for 2 months. Angiographic follow-up was performed at 4, 12 and 24 months, or at 6 and 18 months, depending on the site. Angiographic follow-up is available for 24 patients, and IVUS follow-up is available for 15 patients. Clinical follow-up is available through 2 years.

Demography: Patients had a mean age of 58 years, there were 36% females, 13% had diabetes, 51% of the lesions treated were in the LAD, 22% were in the LCX, 27% were in the RCA, mean reference vessel diameter was 2.9 mm, mean minimum lumen diameter was 0.95 mm, mean percent diameter stenosis was 67%, and 27% of patients had a lesion length < 10 mm and 73% of patients had a lesion length between 10 and 18 mm. Note: IIb/IIIa inhibitor usage was not monitored during this study.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms. Angiographic and IVUS outcomes were assessed by quantitative analysis at designated central laboratories. An independent Clinical Events Committee adjudicated clinical events.

Results: At 18 to 24 months following elective CYPHER™ Stent placement in native coronary *de novo* lesions, in-stent mean % diameter stenosis ranged from 1.4% to 3.2%, and mean in-stent late loss ranged from -0.09 mm to 0.20 mm. Mean obstructive volume by IVUS ranged from 2.3% to 7.5%. The overall MACE rate at 24 months was 10%.

Table XI-3 summarizes the principal effectiveness and safety results of the First-in-Man Study through 24 months.

Table XI-3: First-in-Man: Effectiveness and Safety Results

	CYPHER™ Stent (N=30 Patients, N=30 Lesions)
Effectiveness Measures	
Procedure Success (QCA)	**100.0%** (30/30)
% Diameter Stenosis	
18 Months (The Netherlands)	**3.2%** ± 13.1% (10)
24 Months (Brazil)	**1.4%** ± 5.9% (14)
In-Stent Late Loss (mm)	
18 Months (The Netherlands)	**0.20** ± 0.24 (10)
24 Months (Brazil)	**-0.09** ± 0.24 (14)
Obstruction Volume (%)	
18 Months (The Netherlands)	**2.3%** ± 2.1% (7)
24 Months (Brazil)	**7.5%** ± 7.3% (8)
24-month Target Lesion Revascularization (TLR)	**3.3%** (1/30)
Safety Measures	
In Hospital MACE Events	**6.7%** (2/30)
Out-of-Hospital MACE Events to 24 months	**3.3%** (1/30)
Combined (In and Out-of-Hospital) MACE to 24 months	**10.0%** (3/30)

Numbers are % (counts available field sample size) or Mean ± Standard Deviation.
Procedure Success – The attainment of a final in-stent diameter stenosis of <50% (by QCA) in the absence of death, emergent CABG, Myocardial Infarction, or TLR prior to hospital discharge.
QCA – Quantitative Coronary Angiography by Core lab
MACE is a composite endpoint comprised of deaths, WHO defined non-Q wave myocardial infarction, Q-wave myocardial infarction, or target lesion revascularization.

D. Gender Bias

The gender selection in the SIRIUS and RAVEL studies was random, and based upon exclusion and inclusion criteria. In the SIRIUS pivotal trial (conducted in the US), men represented 71% of the population. In the RAVEL supporting trial (conducted outside of the US), men represented 76% of the population. In the First-in-Man feasibility study (conducted outside of the US), men represented 64% of the population. The ratio of men versus women in each of these trials is reflective of the underlying distribution of the disease for the given age groups, ethnic groups and stages of disease in these populations. No notable differences in safety or effectiveness were found, with respect to gender.

XII. Conclusions Drawn from the Studies

The safety and effectiveness of the Cypher™ Sirolimus-Eluting Coronary Stent System is based on the results obtained from biocompatibility; *in vivo* pharmacokinetics; *in vitro* engineering testing; coating characterization; chemistry, manufacturing and controls information; *in vivo* animal testing; sterilization and stability testing; and clinical studies. These test results revealed the following:

The biocompatibility, *in vivo* pharmacokinetics, and *in vivo* animal testing that were conducted demonstrated that the acute and chronic *in vivo* performance characteristics of the product are safe and acceptable for clinical use.

The *in vitro* engineering testing conducted on the stent and delivery system(s) demonstrated that the performance characteristics met the product specifications and the coating characterization testing adequately described the important attributes of the sirolimus/polymer coating. The chemistry, manufacturing, and controls information ensures that product meeting specifications will be released.

The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The stability testing demonstrated that the product can be labeled with a shelf life of 6 months.

The clinical testing conducted demonstrated that the product provides a reasonable assurance of safety and effectiveness, when used as indicated in accordance with the Instructions for Use.

XIII. Panel Recommendation

At an advisory meeting held on October 22, 2003, the Circulatory Systems Devices Panel unanimously recommended that Cordis Corporation's PMA for the CYPHER™ Sirolimus-eluting Coronary Stent System (OTW and RX) be approved subject to submission, and approval by, the Center for Devices and Radiological Health (CDRH) of the following:

1. The labeling should be restricted to the same as the inclusion criteria for the SIRIUS study (i.e., lengths of 15 to 30mm and diameters of 2.5 to 3.5mm).

2. Modifications to the Instructions for Use should include stronger language regarding the unique aspects of the Cypher™ product (e.g., indicating that this is a combination product of a device and a drug; off-label uses and techniques, such as direct stenting, may have different ramifications than observed for bare metal stents) as deemed appropriate through interaction of the FDA and the sponsor.

3. Modifications to the patient labeling, both in terms of readability and details (e.g., specifics about the drug, issues such as concomitant brachytherapy) as deemed appropriate through interaction of the FDA and the sponsor.

4. Conduct an additional high-dose exposure study, with pharmacokinetic interactions looking at the risk-benefit ratio, to determine the possibility of stent implantation leading to levels that may result in immunosuppression in certain individuals (e.g., those on drugs that are CYP3A4 substrates, etc). As necessary, include appropriate information within the labeling.

5. Specific language to be added to both the patient brochure and physician instructions for use as to the potential hazard and warnings related to adjunctive brachytherapy.

6. Submission of 5-year clinical follow-up on the SIRIUS, RAVEL, and First-In-Man patient populations.

XIV. CDRH Decision

CDRH concurred with the Panel's first recommendation of October 22, 2002, to limit the indications statement to specify the lesion sizes that were actually studied in the clinical studies, including both SIRIUS and RAVEL (i.e., lengths ≤ 30 mm and diameters of 2.5 to 3.5 mm). CDRH also concurred with the Panel's recommendations to revise the labeling (2, 3 and 5) and Cordis Corporation revised the labeling accordingly in a PMA amendment. CDRH also concurred with the Panel's sixth recommendation for longer-term follow-up on patients enrolled in the pivotal, supportive and feasibility studies and this was included as a condition of approval within the approval order for the PMA.

In consideration of the Panel's fourth recommendation of October 22, 2002, the sponsor submitted supplemental PK and drug interaction information in PMA amendments. Based upon the review of this information by CDER and CDRH, in conjunction with available Cmax data from PK studies conducted with the CYPHER™ Stents, an additional study was not found to be necessary to adequately address this issue. Appropriate language was included within the labeling (submitted as a PMA amendment) regarding the usage of longer or multiple stents and drug-drug interactions with drugs which are substrates for CYP3A4, which could potentially increase systemic concentrations of sirolimus to approach immunosuppressive levels temporarily in some patients. Please refer to the product labeling for specific language included.

This PMA application was designated for expedited review on June 28, 2002 by CDRH since it was determined that the CYPHER Stent could represent a breakthrough technology which offers a viable alternative to FDA approved technologies for treating occlusive coronary artery disease. This PMA application sought approval for the first drug-eluting coronary stent system.

The applicant's manufacturing and sterilization facilities completed inspections on the following dates:

- March 9, 2001 (Miami Lakes, FL)
- July 13, 2001 (Roden, The Netherlands)
- July 26, 2001 (San Angelo, TX)
- September 11, 2002 (Warren, NJ)
- September 19, 2002 (Somerville, NJ)
- September 26, 2002 (Latina, Italy)
- October 3, 2003 (Beerse, Belgium)
- April 16, 2003 (San German, Puerto Rico)

The inspections of these facilities were found to be in compliance with relevant device Good Manufacturing Practice (GMP) regulations and pharmaceutical current Good Manufacturing Practice (cGMP) regulations.

FDA issued an approval order on April 24, 2003.

XV. Approval Specifications

Directions for Use: See product labeling.

Hazard to Health from Use of the Product: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Post Approval Requirements and Restrictions: See Approval Order.